REMARKS

FORMAL MATTERS

Claims 132-152 are pending after entry of the amendments set forth herein.

Claims 85-131 are cancelled without prejudice to renewal.

Claims 132-152 are newly added. Support for new claims 132-150 is found throughout the instant specification, particularly at the following positions: page 5, lines 17-27; page 6, line 1; page 7, lines 13-14; page 4, lines 15-17; page 57, line 2; page 4, lines 15-17; page 56, line 29 to page 57, line 2; page 6, line 22; page 4, lines 15-19; page 25, lines 25-29; page 9, lines 10-12; page 10, line 12 to page 13, line 8; page 4, lines 20-22; page 78, Example 8; page 10, line 12 to page 13, line 8; page 8, lines 19-23; page 6, line 1; page 82, lines 1-4; page 36, lines 33-35; page 43, lines 9-17, page 63, line 31 to page 64, line 15; and page 10, line 12 to page 11, line 8.

No new matter is added.

INFORMATION DISCLOSURE STATEMENT

This communication is submitted in conjunction with an Information Disclosure Statement.

The Examiner is requested to initial the accompanying PTO-SB/08A form, thereby indicating that the references cited in the Information Disclosure Statement have been reviewed and made of record.

RESTRICTION REQUIREMENT

The Applicants acknowledge and appreciate the Examiner's decision to rejoin SEQ ID NO:2 with the elected subject matter.

The Applicants maintain their position that the basis for the Examiner's requirement for restriction is erroneous.

In particular, the Applicants note that the Examiner's refusal to rejoin SEQ ID NO:5 with SEQ ID NO:3 is erroneous. The Examiner's statement that "SEQ ID NO:5 does not

share a significant common feature with SEQ ID NO:2 and 3" (page 2, second full paragraph) is erroneous, as SEQ ID NO:5 is disclosed to be a mouse RUP41 G protein-coupled receptor, and features common to G protein-coupled receptors are set forth at page 2 line 33-page 3 line 9 of the application as filed. Furthermore, as indicated in our September 26, 2006, response to the Restriction Requirement, SEQ ID NO:5 is about 95% identical to SEQ ID NOS:2 and 3.

A Petition to the Director under 37 CFR § 1.181 requesting review of the Restriction Requirement will be filed in due course.

DRAWINGS

The Examiner objects to the drawings because the drawings are allegedly not clear.

Replacement sheets of drawings are submitted herewith.

The Examiner is requested to review the drawings and indicate whether the drawings are satisfactory.

If this objection is maintained, the Examiner is requested to indicate which drawing in particular is unclear, and why that drawing is unclear, so that the objection can be adequately addressed.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 101

Claims 85-96 and 122-131 are rejected under 35 U.S.C. § 101 as allegedly having no patentable utility. The Applicants traverse this rejection as applied to new claims 132-150.

The standard for meeting the utility requirement of 35 U.S.C. § 101 for biotechnology-related inventions is discussed in great detail in MPEP § 2107.03.

According to MPEP § 2107.03:

"If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process." (Emphasis added).

The Examiner is referred to the underlined portion of the above: "data generated from *in vitro* assays almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

The Applicants teach throughout the instant specification that increasing RUP41 activity confers cardioprotection. For example, the instant specification provides *in vitro* data demonstrating that increasing RUP41 activity by overexpressing constitutively active RUP41: a) rescues cultured heart muscle cells (myocytes) from death associated with hypoxia followed by reoxygenation (Example 17), and b) promotes survival of cultured heart muscle cells (Example 16). The skilled artisan at the time of filing would be aware that in the adult heart myocyte, death is a critical element of the natural history of heart failure (see, e.g., the first full paragraph of Katz, Heart Failure, 2000, Lippincott Williams & Wilkins; reference in accompanying IDS).

Given that the MPEP explicitly states that *in vitro* data is almost invariably sufficient to establish utility, and *in vitro* demonstrating that RUP41 has a utility in cardioprotection is provided in the instant specification, the Applicants submit that no more data need be provided to establish a patentable utility.

Although not necessary given that the MPEP indicates that no more than data from *in vitro* assays should be required to establish a patentable utility, the specification also provides data showing that RUP41 is down-regulated in: cultured heart cells that are stressed (Example 11), mouse hearts that are stressed (Example 12), cultured heart cells that are hypoxic (Example 13) and hearts from human patients having congestive heart failure (Example 14). As such, in addition to the above-described *in vitro* data, the specification also provides corroborative *in vivo* data, including data from *human* patients, that confirm RUP41's utility in cardioprotection.

In the Office Action, the Examiner alleges that the claims of this case have no utility for various reasons, namely: a) the natural RUP41 ligand is not known, b) there is no known causative link between RUP41 and heart disease, c) there is no disclosure of examples of compounds (e.g., agonists of RUP41) that can be used to treat heart disease, and d) there are no identifying characteristics for compounds that can be used to treat heart disease.

However, it is clear from MPEP § 2107.03 that the reasons cited by the Examiner are insufficient to establish this rejection.

The Applicants submit that this rejection has been adequately addressed. Withdrawal of this rejection is respectfully requested.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, ¶1 (UTILITY)

Claims 85-96 and 122-131 are rejected under 35 U.S.C. §112, first paragraph, because they are rejected under 35 U.S.C. §101.

The Applicants respectfully submit that this rejection should be withdrawn along with the §101 rejection for the reasons outlined above.

Withdrawal of this rejection is requested.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, ¶1 (ENABLEMENT)

Claims 85-96 and 122-131 are rejected for allegedly failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph. The Applicants traverse this rejection as applied to new claims 132-150.

Many aspects of this rejection, particularly those relating to prevention of cardiovascular disorders and candidate compounds that are modulators of cardioprotection are believed to be rendered moot by the provision of a new set of claims.

With respect to the Examiner's argument that it is impossible to practice the claimed method without first making a constitutively active version of RUP41, the Examiner is reminded that the *wild-type* RUP41: a) is constitutively active; b) increases the longevity of cultured heart muscle cells; and c) rescues cultured heart muscle cells from death associated with hypoxia followed by reoxygenation, as shown in Examples 15, 16 and 17 of the specification. As such, the Examiner's argument carries no weight.

The remaining aspect of this rejection, which relates to enablement of a genus of polypeptides, is addressed below.

It is the Applicant's understanding from a review of the Office Action that although two distinct and separate rejections are made under 35 U.S.C. §112, first paragraph, many of the issues that underpin both of the rejections are related, somewhat overlapping, and largely relate to the structural and functional characteristics of the polypeptides recited in the claims. As such, while the Applicants understand that the written description requirement of 35

U.S.C. §112 is separate and distinct from the enablement requirement of 35 U.S.C. §112[1] and that patentable subject matter needs to satisfy both requirements, the Applicant believes that both rejections can be addressed by a single discussion. In view of the above, the Examiner is requested to apply the following arguments to both of the rejections under 35 U.S.C. §112, first paragraph, as elaborated in this Office Action.

The rejected claims are directed to a screening method that employs a G protein-coupled receptor comprising an amino acid sequence having at least 90% identity to SEQ ID NO:3, a wild type human RUP41.

The basis for these rejections relates in large part to the claims encompassing variants of the human polypeptides that are explicitly disclosed in the specification. The questions are whether such molecules are adequately described in the specification, and whether one of skill in the art would make and use such molecules without undue experimentation.

In response, the Examiner is respectfully directed to: a) page 2, line 33 to page 3, line 19 of the instant specification, where the structure/function relationship of GPCRs is described; b) page 4, lines 35 to page 5, line 4 of the instant specification, where two allelic variants of human RUP41, and a RUP41 from mouse are discussed; c) page 56, lines 10-12, where the specification provides guidance for making constitutively active mutants of RUP41; and d) the section starting on page 40, where a variety of methods for assaying GPCRs (which can be used to test variant proteins) are described in detail.

Further, as shown in Exhibit A, a search of NCBI's PubMed database reveals that there are well over 2900 journal articles, including 450 reviews, that have a publication date that precedes the priority date of the instant application (August 1, 2002) and contain the phrase "GPCR" OR "G protein-coupled receptor" in the abstract. Thus, at the priority date of the instant application, GPCR proteins were a subject of significant interest in the scientific community. The art in which the subject RUP41 protein belongs was therefore highly developed at the priority date of the instant application. For example, at the priority date of the instant application one of skill in the art would have knowledge of the atomic coordinates of at least one GPCR (see, e.g., reference A listed on Exhibit B). At the time of filing, the

[1] *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977).

structure/function relationship of many GPCRs had been investigated (see, e.g., references B-H listed on Exhibit B), and several reviews on the structure/function relationship of GPCRs had been published (see, e.g., references I-O listed on Exhibit B)

In addition, at the time of filing, one of skill in the art would have been aware of several algorithms for predicting GPCR structure (see, e.g., references P and Q listed on Exhibit B), an algorithm for predicting important residues in GPCRs (see, e.g., reference R listed on Exhibit B), and reviews on the engineering of GPCRs by domain swapping (see, e.g., references S and T listed on Exhibit B).

Given the vast amount of available information on structure/function relationships in GPCR proteins in general, in combination with the structure/function information on RUP41 in the instant specification, the Applicant submits that one of skill in the art would be able to envision a large number of operable variants of RUP41, and be able to use those variants without undue experimentation.

The Applicant understands that the effect of amino acid and nucleotide substitutions cannot be predicted with absolute certainty. However, given the information in the instant specification and the deep general understanding of the structure and function of GPCR proteins, the Applicant submits that such molecules are more than adequately described and enabled.

The Applicant submits that these rejections have been adequately addressed. Withdrawal of these rejections is requested.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, ¶1 (WRITTEN DESCRIPTION)

Claims 85-96 and 122-131 are rejected for allegedly failing to meet the written description requirement of 35 U.S.C. §112, first paragraph. The Applicants traverse this rejection as applied to new claims 132-150.

This rejection is addressed in the previous section of this response.

Withdrawal of this rejection is respectfully requested.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, ¶2 (INDEFINITENESS)

Claims 85-96 and 122-131 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite.

Without conceding to the correctness of this rejection and solely to expedite prosecution, claims 85-96 and 122-131 are cancelled.

The phrases in question are not present newly presented claims. As such this rejection is moot and may be withdrawn.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 102

Claims 85-93, 95, 96, 122-129 and 131 under 35 U.S.C. § 102(e) as allegedly anticipated by Liaw. The Applicants traverse this rejection as applied to new claims 132-150.

The Applicants submit that Liaw fails to disclose element c of claim 1, i.e., determining if a compound has cardioprotective activity. As such, Liaw cannot anticipate the claims, and this rejection should be withdrawn.

Withdrawal of this rejection is requested.

CLAIM OBJECTIONS

Claims 85-96 and 122-131 are objected to for allegedly reciting non-elected subject matter.

The language to which the Examiner rejects no longer appears in the claims. As such, this rejection is believed to be moot.

Withdrawal of this rejection is requested.

Conclusion

A timely Notice of Allowance is requested.

If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AREN-027.

Respectfully submitted,
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Date: June 8, 2007

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10/523,100 Exhibit A

Limits: **Entrez Date from 1980/01/01 to 2002/07/31**

1: Medkova M, Preininger AM, Yu NJ, Hubbell WL, Hamm HE. Related Articles, Links

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PMID: 12146960 [PubMed - indexed for MEDLINE]

2: Hengge UR, Ruzicka T, Tyring SK, Stuschke M, Roggendorf M, Schwartz RA, Seeber S. Related Articles, Links

Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 2: pathogenesis, Castleman's disease, and pleural effusion lymphoma.
Lancet Infect Dis. 2002 Jun;2(6):344-52. Review.
PMID: 12144897 [PubMed - indexed for MEDLINE]

3: Whistler JL, Enquist J, Marley A, Fong J, Gladher F, Tsuruda P, Murray SR, Von Zastrow M. Related Articles, Links

Modulation of postendocytic sorting of G protein-coupled receptors.
Science. 2002 Jul 26;297(5581):615-20.
PMID: 12142540 [PubMed - indexed for MEDLINE]

4: Zhang N, Long Y, Devreotes PN. Related Articles, Links

Ege A, a novel C2 domain containing protein, is essential for GPCR-mediated gene expression in dictyostelium.
Dev Biol. 2002 Aug 1;248(1):1-12.
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5: Nickenig G. Related Articles, Links

Central role of the AT(1)-receptor in atherosclerosis.
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PMID: 12140725 [PubMed - indexed for MEDLINE]

6: Poronnik P, Cummins MM, O'Mullane LM, Cook DI. Related Articles, Links

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Cell Biochem Biophys. 2002;36(2-3):221-33. Review.
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EXHIBIT B

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B. Shin N et al, *Molecular modeling and site-specific mutagenesis of the histamine-binding site of the histamine H4 receptor.* Mol Pharmacol. 2002 62:38-47.

C. Chung DA et al, *Mutagenesis and peptide analysis of the DRY motif in the alpha2A adrenergic receptor: evidence for alternate mechanisms in G protein-coupled receptors.* Biochem Biophys Res Commun. 2002 293:1233-41.

D. Mouledous et al, *Functional inactivation of the nociceptin receptor by alanine substitution of glutamine 286 at the C terminus of transmembrane segment VI: evidence from a site-directed mutagenesis study of the ORL1 receptor transmembrane-binding domain.* Mol Pharmacol. 2000 57:495-502.

E. Krasnoperov et al, *Structural requirements for alpha-latrotoxin binding and alpha-latrotoxin-stimulated secretion. A study with calcium-independent receptor of alpha-latrotoxin (CIRL) deletion mutants.* J Biol Chem. 1999 274:3590-6.

F. Hurley et al, *Structure-function studies of the eighth hydrophobic domain of a serotonin receptor.* J Neurochem. 1999 72:413-21

G. Akal-Strader et al, *Residues in the first extracellular loop of a G protein-coupled receptor play a role in signal transduction.* J Biol Chem. 2002 277:30581-90.

H. Yang et al, *Molecular determinants of human melanocortin-4 receptor responsible for antagonist SHU9119 selective activity.* J Biol Chem. 2002 277:20328-35

I. Ulloa-Aguirre et al, *Structure-activity relationships of G protein-coupled receptors.* Arch Med Res. 1999 30:420-35 (Review)

J. Chollet et al, *Biophysical approaches to G protein-coupled receptors: structure, function and dynamics*. J Comput Aided Mol Des. 1999 13:209-19 (Review)

K. Gimpl et al, *The oxytocin receptor system: structure, function, and regulation.* Physiol Rev. 2001 81:629-83 (Review)

L. Bai et al, *Structure and function of the extracellular calcium-sensing receptor*. Int J Mol Med. 1999 4:115-25 (Review)

M. Olah et al, *The role of receptor structure in determining adenosine receptor activity*. Pharmacol Ther. 2000 85:55-75 (Review)

N. Missale et al, *Dopamine receptors: from structure to function*. Physiol Rev. 1998 78:189-225 (Review)

O. Sealfon et al, *Functional domains of the gonadotropin-releasing hormone receptor.* Cell Mol Neurobiol. 1995 15:25-42 (Review)

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Q. Orry et al, *Modeling and docking the endothelin G-protein-coupled receptor.* Biophys J. 2000 79:3083-94.

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T. Gouldson et al, *Dimerization and domain swapping in G-protein-coupled receptors: a computational study*. Neuropsychopharmacology. 2000 23:S60-77.